Ventricular Arrhythmias in Congestive Heart Failure

Clinical Significance and Management

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Ventricular arrhythmias are frequently encountered in patients with left-ventricular dysfunction and congestive heart failure. Approximately 1% to 2% of the United States population, or approximately 2 to 3 million people, suffer from congestive heart failure (CHF).[1-4] Approximately 250,000 to 400,000 new cases are reported annually.[1-4] Ventricular premature depolarizations (VPDs) occur in 70% to 95% of heart failure patients, and nonsustained ventricular tachycardia occurs in 20% to 80% (Table I).[6,9,10,18-21] Also, 50% to 60% of deaths in patients with CHF are sudden and are attributed to an arrhythmic cause, most often to ventricular tachyarrhythmia.[7,22-24]

While ventricular arrhythmias are not always symptomatic, their ultimate clinical effect is an increased risk of sudden cardiac death and a higher overall mortality rate. Controversy is ongoing regarding the management of ventricular arrhythmias in different clinical settings, despite lessons learned from several recent clinical trials. This review summarizes the data that are currently available and controversies found in the literature regarding the prognostic significance and the management of ventricular arrhythmias in patients with left-ventricular (LV) dysfunction and CHF.

Significance and Prognostic Value of Ventricular Arrhythmias

Ventricular Premature Depolarizations. Patients with systolic or diastolic LV dysfunction, regardless of the cause, have an increased incidence of VPDs.[25,26] Contributory factors include fibrotic myocardium, abnormal wall stress, heightened sympathetic tone, and electrolyte abnormalities. The majority of studies have found that complex, frequent VPDs are associated with an increased overall mortality rate, and several studies have also noted an association with sudden death. However, the increased risk might be due to severe ventricular dysfunction rather than arrhythmias. Because of the electrophysiologic differences between nonischemic heart failure and ischemic heart failure, these 2 conditions will be discussed separately. The frequency of VPDs (ventricular ectopic activity) in patients with cardiomyopathy, whether ischemic or nonischemic, is shown in Table I.

In patients who have suffered a prior myocardial infarction (MI), frequent or complex VPDs constitute an independent predictor of death; in some studies they have been found to constitute an independent predictor of sudden death.[27] Bigger and associates[28] examined the relationship between ventricular arrhythmias, LV dysfunction, and 2-year mortality in 766 patients who had suffered MI. Ventricular arrhythmia was found to be an independent predictor of arrhythmic death, and the highest risk was associated with pairs or runs of VPDs. See Table II.

The Coronary Drug Research Project[29] performed rhythm strips for an average of 49 beats in MI survivors at their 1st office visit. During a 3-year follow-up period, the mortality and sudden death rates of patients with VPDs were found to be twice as high as those of patients without VPDs. Although these numbers were impressive, the effect of complex VPDs on the rate of sudden death independent of LV dysfunction was not defined until several years later. The Multicenter Investigation of the Limitation of Infarct Size (MILIS)[30] reported that a finding of 10 or more VPDs per hour on 24-hour ambulatory electrocardiography on the 10th day after MI was an independent risk factor for sudden cardiac death. Further, the Multicenter Postinfarction Research Group study[28] showed that a VPD

TABLE I. Prevalence of Ventricular Arrhythmias in Patients with Congestive Heart Failure

Study	No. of Patients	Diagnosis	CHF(%)	VEA(%)	NSVT(%)
Huang et al, 1983[5]	35	DCM	60	93	60
Wilson et al, 1983[6]	77	CAD/DCM	100	71	50
Meinertz et al, 1984[7]	74	DCM	100	87	49
von Olshausen et al, 1984[8]	60	DCM	100	95	42
Maskin et al, 1984[9]	35	CAD/DCM	100	92	71
Holmes et al, 1985[10]	31	CAD/DCM	100	87	39
Chakko et al, 1985[11]	43	CAD/DCM	100	88	51
Francis, 1986[2]	346	CAD/DCM	100	81	28
Unverferth et al, 1984[12]	69	DCM	100	91	25
Costanzo-Nordin et al, 1985[13]	55	DCM	87	85	40
Neri et al, 1987[14]	65	DCM	100	95	80
Gradman et al, 1989[15]	295	CAD/DCM	100	59	36
Keogh et al, 1990[16]	137	CAD/DCM	100	39	41
Range				39-95	25-80
Total	1322			82	47

CAD = coronary artery disease; CHF = congestive heart failure; DCM = dilated cardiomyopathy; NSVT = nonsustained ventricular tachycardia; VEA = ventricular ectopic activity

(From: Waxman HL, et al. Congestive heart failure, cardiomyopathy, and ventricular arrhythmia.[17] Reproduced by permission.)

TABLE II. Relationship among Repetitive Ventricular Premature Depolarizations, Left Ventricular Ejection Fraction, and 2-Year Mortality in Survivors of Myocardial Infarction (n = 766)

LVEF	Repetitive VPDs*				Total
	None	Singles	Pairs	Runs	
<30%	22% (9)	21% (58)	39% (24)	42% (26)	30% (117)
30-39%	17% (6)	10% (84)	8% (30)	16% (19)	10% (139)
40-49%	0% (31)	7% (113)	12% (38)	23% (10)	7% (192)
≥50%	5% (56)	7% (191)	11% (38)	12% (33)	7% (318)
Total	6% (102)	9% (446)	16% (130)	23% (88)	11% (766)

* Percent values are the Kaplan-Meier survivorship estimates of 2-year mortality rates. Numbers in parentheses are the numbers of patients in that category at the start of follow-up.

LVEF = left ventricular ejection fraction; VPD = ventricular premature depolarization

(From: Bigger JT Jr, et al. The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction.[28] Reproduced with permission.)

frequency of more than 3 per hour was sufficient to independently predict increased rates of overall mortality and sudden death.

Much less is known about the association between VPDs and sudden death in patients with CHF caused by idiopathic cardiomyopathy.[31-35] Ventricular premature depolarizations and nonsustained ventricular tachycardia have been related to overall mortality and sudden cardiac death in some, but not all studies. Although VPDs are likely markers for worse LV function and lower overall survival rates, their association with increased risk for sudden cardiac death is still controversial.[5,7,36-38]

In summary, in patients with CHF caused by coronary artery disease, VPDs seem to constitute an independent risk factor for sudden cardiac death and total mortality. This relationship is not as well established in patients with idiopathic dilated cardiomyopathy.

Nonsustained Ventricular Tachycardia. Nonsustained ventricular tachycardia (NSVT)—defined as runs of 3 or more consecutive VPDs faster than 100 beats per minute that terminate spontaneously within 30 seconds—is a very common finding in CHF patients (Table III).[5,7,36-38] In most studies, the prevalence of NSVT is determined from 24-hour or, at most, 48-hour Holter monitoring. Most episodes of NSVT are found incidentally during inpatient monitoring or outpatient Holter studies. The actual occurrence of this arrhythmia might be underestimated because the typical monitoring period is of short duration. Although NSVT may be discovered during the evaluation of palpitations, presyncope, chest pain, or syncope,[46-49] most episodes do not correlate with these symptoms, because of the brief duration of the arrhythmia.

Approximately 50% of patients with nonischemic dilated cardiomyopathy have asymptomatic NSVT [28,41,43,50,51]; this represents the highest prevalence of NSVT among any patient group. Studies have reported a correlation between increased prevalence of NSVT and more advanced disease.[28,41,43,50,51]

TABLE III. Epidemiologic Studies Demonstrating Association between Presence of Nonsustained Ventricular Tachycardia (NSVT) and Mortality Risk

Study	Type of Heart Disease	No. of Patients Studied	Mortality (%)	
			(NSVT+)	(NSVT−)
Anderson et al.[39]	CAD/Post-MI	915	16	8
Kleiger et al.[40]	CAD/Post-MI	289	17	6
Bigger et al.[41]	CAD/Post-MI	430	54	19
Bigger et al.[28]	CAD/Post-MI	766	25	6
Denes et al.[42]	CAD/Post-MI	755*	15	8
Maggioni et al.[43]	CAD/Post-MI	8676	5	3
de Soyza et al.[44]	CAD/Post-MI	56	6	18
Meinertz et al.[7]	DCM	74	N/A	N/A
Huang et al.[5]	DCM	35	14	7
Olshausen et al.[38]	DCM	73	†36/16	†5/19
Savage et al.[26]	HCM	100	‡ 10	‡ 0
McKenna et al.[45]	HCM	86	‡ 21	‡ 3
Holmes et al.[10]	CAD, DCM	31	59	11
Unverferth et al.[12]	DCM	69	45	0
Wilson et al.[6]	CAD, DCM	77	N/A	N/A

* = patient receiving active therapy with encainide/flecainide only
† = pump failure death/sudden death
‡ = sudden death

CAD = coronary artery disease; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; N/A = not stated; NSVT+ = NSVT present; NSVT− = NSVT not present; Post-MI = post-myocardial infarction

(From: Marinchak RA, Rials SJ, Filart RA, Kowey PR. The top ten fallacies of nonsustained ventricular tachycardia. Pacing Clin Electrophysiol 1997;20:2825-47. Reproduced with permission from Futura Publishing Co. Inc.)

In patients with coronary artery disease, irrespective of LV function, the highest prevalence of NSVT is seen in the 1st 24 hours after the onset of acute MI, when as many as 45% of patients have been reported to have this arrhythmia.[52,53] The prevalence then drops to 7% to 16% during the late hospital phase (1 to 4 weeks after the onset of MI),[54-56] and remains fairly constant over the 1st year after MI. In patients with coronary artery disease combined with a low ejection fraction, the prevalence of NSVT is much higher.[57-60] The prevalence of NSVT is also increased among patients with multivessel disease, regional wall motion abnormality, or coexistent ventricular aneurysm.[57-60]

Nonsustained ventricular tachycardia is an independent risk factor for both overall cardiac death and sudden cardiac death among patients with underlying coronary artery disease.[39,54,56,61,62] The prognostic significance of NSVT in combination with underlying coronary artery disease depends on when the arrhythmia is discovered during the course of the disease. The occurrence of NSVT during the 1st 24 hours after MI does not carry an increased risk for overall mortality or sudden cardiac death.[53,63,64] However, for patients who experience NSVT in the late hospital phase of MI, the risk of sudden death is more than twice as high as it is for patients without NSVT. Detection of NSVT 3 months to 1 year after MI is also associated with a significantly higher mortality rate.[65-67] However, while NSVT combined with coronary artery disease is associated with increased rates of overall cardiac-related mortality and sudden cardiac mortality, the proportion of sudden cardiac deaths to overall mortality is not increased. This suggests that NSVT is a marker of overall cardiac function rather than a marker for subsequent arrhythmic events.[54,62,68,69] Further, the use of data from episodes of NSVT (i.e., frequency, duration, rate) to predict death, or to predict the likelihood of inducing or developing spontaneous sustained ventricular tachycardia, has never been substantiated. This lack of definite correlation has been shown repeatedly in studies of post-MI patients and in the preliminary data from the ongoing MUSTT* trial.[39,41-43,62,70]

When compared with the number of studies that have focused on the post-MI population, the number of studies that have focused on the more heterogeneous group of patients with NSVT and nonischemic heart disease is relatively small. Patients with nonischemic dilated cardiomyopathy are at considerable risk of cardiac-related death and sudden cardiac death, with 1-year mortality rates as high as 40% to 50%.[43,71,72] However, the prognostic significance of NSVT among these patients is variable—there is little evidence that NSVT is related specif-

ically to an increased risk of sudden death, but it does correlate with increased rates of overall cardiac-related mortality.[5,20,21,73-75] To our knowledge, only 1 study of patients with nonischemic dilated cardiomyopathy has found that patients who died suddenly had experienced a higher frequency of NSVT episodes than had patients who died from worsening CHF. The preliminary data from the MUSTT trial and subanalyses of the BHAT* and CHF-STAT* studies have all failed to show a statistically significant correlation between the presence of NSVT and subsequent sudden cardiac death in patients with dilated nonischemic cardiomyopathy. It seems that the increased overall mortality rates in some of these studies indicate that NSVT is a marker of a more severe disease process rather than of a terminal electrical event.

Sustained Ventricular Tachycardia. Sustained monomorphic ventricular tachycardia occurs in approximately 9% of patients with advanced heart failure who are referred for cardiac transplantation.[16] In patients with ischemic heart failure, there is considerable evidence that these tachycardias have reentrant mechanisms caused by scarring within the myocardium, and there is a high rate of inducibility by programmed electrical stimulation.[76] Conversely, in patients with nonischemic dilated cardiomyopathy, sustained monomorphic ventricular tachycardia is rare and is not easily provoked by programmed electrical stimulation. In these patients, the mechanism of ventricular tachycardia may be triggered activity as well as reentry.[77] Potential contributing factors are electrolyte depletion from chronic diuretic therapy, excessive activation of the sympathetic nervous and renin angiotensin systems, and proarrhythmic effects of certain medications.

Patients who experience sustained ventricular tachycardia are at high risk for recurrent arrhythmia and sudden cardiac death.[78] However, the risk of death is lower (2% to 3% mortality per year) for patients in whom the ventricular tachycardia is hemodynamically tolerated. For this reason, most primary and secondary implantable cardioverter-defibrillator (ICD) prevention trials have excluded patients with hemodynamically stable ventricular tachycardia.

In patients with hemodynamically unstable ventricular tachycardia and nonischemic dilated cardiomyopathy, the incidence of sudden cardiac death may be as high as 50%, but the majority of deaths are associated with ventricular fibrillation rather than sustained monomorphic ventricular tachycardia. Poll and colleagues[79] reported that in a group of 13 patients who presented with sustained monomorphic ventricular tachycardia, ventricular tachycardia could

*MUSTT = Multicenter Unsustained Tachycardia Trial

*BHAT = β-Blocker Heart Attack Study; CHF-STAT = Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure

be induced in all of the patients at electrophysiology study, and 4 of the 13 patients died suddenly during the follow-up period. Brembilla-Perrot and coworkers[80] induced sustained monomorphic ventricular tachycardia in 8 of 11 patients with dilated cardiomyopathy who presented with this arrhythmia. The recurrence rate of sudden cardiac death or ventricular tachycardia was 60% in patients with nonsuppressible ventricular tachycardia, but 20% in those with suppressible ventricular tachycardia. These data suggest that if ventricular tachycardia is suppressible, the risk of sudden cardiac death is reduced.

Sudden Death and CHF. Left-ventricular dysfunction is a major independent predictor of sudden and total cardiac death in patients with ischemic or nonischemic cardiomyopathy.[6,28,81,82] For the cardiac arrest survivor whose left-ventricular ejection fraction (LVEF) is less than 30% and who does not have inducible ventricular tachycardia, the risk of sudden cardiac death exceeds 30% over a period of 1 to 3 years; if the patient has inducible ventricular tachyarrhythmia, the risk of sudden cardiac death ranges between 15% and 50%, despite therapy with drugs that suppress the inducible arrhythmia or with empiric amiodarone.[83-85] Severe LV dysfunction is an independent predictor of death, but unfortunately it does not distinguish patients who will die suddenly from those who will die of progressive CHF.[6,81,86]

Approximately 10% of sudden cardiac deaths in the adult population occur in patients with idiopathic dilated cardiomyopathy (IDCM). Mortality rates among patients with IDCM are high, reaching 10% to 50% annually, depending on the severity of disease.[87] An overview of 14 studies that included a total of 1,432 patients with IDCM reported a mean mortality rate of 42% after a 4-year follow-up period, and 28% of the deaths were classified as sudden.[87] Sudden cardiac death in patients with IDCM is usually attributed to ventricular tachyarrhythmias because of the high frequency of complex ventricular ectopic activity in these patients.[25] However, the terminal event can also be asystole or electromechanical dissociation, especially in patients with advanced LV dysfunction.[57] It seems that in more advanced cases of heart failure, bradyarrhythmias and electromechanical dissociation play a more significant role than was previously thought, and this may explain the limited success of ICDs in patients with advanced heart failure. The results of the MUSTT trial are likely to shed more light on this matter.

Risk Stratification

Several invasive and noninvasive tests have been used to stratify patients with ventricular arrhythmias according to their risk. While a complete presentation of these tests is beyond the scope of this article, we discuss the roles of programmed electrical stimulation (PES) and signal-averaged electrocardiography (SAECG) in the risk stratification of patients with LV dysfunction and ventricular arrhythmias. These 2 tests were selected for discussion because of their use in current clinical trials.

Programmed Electrical Stimulation

The value of PES in the evaluation and management of patients with depressed LV function and coronary artery disease has been proved. However, its beneficial role in the risk stratification of patients with nonischemic cardiomyopathy has not been proved.[79,88-91]

Ventricular Dysfunction and Coronary Artery Disease. Bourke and coworkers[92] studied patients 6 to 28 days after MI, and found that ventricular tachycardia inducible by PES was uncommon in patients whose LVEF was greater than 40%; however, ventricular tachycardia was inducible by PES in 36% of patients whose LVEF was less than 25%. The likelihood of spontaneous sustained ventricular tachycardia or sudden death during the 1st year after MI was 19% in patients with inducible tachycardia, and 2.9% in patients without inducible ventricular tachycardia.

Wilber and coworkers[93] studied 100 post-MI patients with NSVT and LVEF less than 40%, and were able to initiate sustained monomorphic ventricular tachycardia in 37% of the patients; polymorphic ventricular tachycardia or ventricular fibrillation was induced in another 6%. All of the patients with inducible ventricular tachycardia were treated with antiarrhythmic drugs, and 3 of them suffered their 1st spontaneous cardiac arrest shortly after beginning antiarrhythmic drug therapy. During a 2-year follow-up period, sudden death occurred in 6% of patients who did not have inducible ventricular tachycardia, and in 20% of patients who had inducible ventricular tachycardia treated with antiarrhythmic drugs. Twenty of the patients with inducible tachycardia received drugs that slowed but did not suppress inducible tachycardia, and another 20 patients were treated with drugs that suppressed it. The likelihood of sudden death was greater for those whose inducible tachycardia was not suppressed (35% vs. 10%). It is possible that antiarrhythmic therapy contributed to the deaths, but this study suggests that patients with depressed ventricular function and inducible ventricular tachycardia have a higher risk of spontaneous ventricular tachycardia than do patients without inducible ventricular tachycardia.

Other studies[93-96] have also reported that arrhythmic event rates were less than 10% in patients without inducible sustained ventricular tachycardia, even when LVEF was less than 40%. In another study[97] of 24 consecutive patients with more advanced ven-

tricular dysfunction late after MI who had not suffered spontaneous ventricular tachycardia, sustained monomorphic ventricular tachycardia could be initiated by PES in only 20% of the patients; however, even the patients without inducible tachycardia demonstrated a sudden death rate of 26% during the next year.

In summary, the data that are currently available indicate that sustained ventricular tachycardia can be induced by PES in as many as 40% to 50% of post-MI patients with NSVT.[93,94,96] If the induced arrhythmia is not suppressed with an antiarrhythmic drug, the risk for development of spontaneous ventricular tachycardia or ventricular fibrillation, or both, is significantly higher when compared to patients for whom an effective drug is identified (2-year event rates: 35% to 64% for patients with nonsuppressible arrhythmia; 5% to 20% for patients with suppressible arrhythmia).[93,94,96] The likelihood of finding an effective drug is about 50% to 75%, and is substantially greater in patients who have already suffered spontaneous ventricular tachycardia or ventricular fibrillation.[93,94,96,98,99] The initiation of polymorphic ventricular tachycardia or ventricular fibrillation in the electrophysiology lab is nonspecific and does not reveal any prognostic information.[100] On the basis of these data, PES was selected as a risk stratification test by investigators in the MADIT* trial, which is discussed later in this article.

Nonischemic Cardiomyopathy. In patients with advanced ventricular dysfunction caused by nonischemic dilated cardiomyopathy, induction of ventricular tachycardia by PES is uncommon but the risk of sudden death is high. In those who have not already suffered spontaneous sustained ventricular tachycardia, studies have failed to show a correlation between the inducibility of sustained ventricular tachycardia/ventricular fibrillation and subsequent spontaneous sustained ventricular tachycardia/ventricular fibrillation or cardiac-related death.[88,97-100] A study of 194 patients in 6 centers reported that sustained monomorphic ventricular tachycardia was induced in 4% of the patients. Despite the low incidence of inducible tachycardia, 14% of the patients died suddenly during average follow-up periods of less than 2 years.

Since the introduction of ICDs as the 1st line of therapy in patients with life-threatening arrhythmias, several investigators have questioned the use of electrophysiology studies for risk stratification.[101] According to these investigators,[101] as many as 30% of cardiac arrest survivors and patients with symptomatic sustained ventricular tachycardia have no inducible arrhythmia at baseline electrophysiology study; therefore, the efficacy of drug therapy cannot

*MADIT = Multicenter Automatic Defibrillator Implantation Trial

be assessed. And for those patients in whom arrhythmia is induced, it is suppressed by electrophysiology-guided drug therapy in only 20% to 50% of cases.[102] Therefore, in the majority of these patients, ventricular tachyarrhythmia is either not inducible at baseline or is not suppressible by drug therapy. These patients, by virtue of their presenting symptom, have a high risk of subsequent arrhythmic events and need defibrillator therapy.

Further, electrophysiology studies are poor predictors of the efficacy of drug therapy in patients with poor LV function (ejection fraction less than 30%)[101] and substrates other than chronic coronary atherosclerosis.[103,104] Most importantly, the sudden death rate seems to be higher in these patients than in patients who undergo primary ICD implantation, even when ventricular tachyarrhythmia is suppressed by electrophysiology-guided drug therapy.[105,106]

Summary. Programmed electrical stimulation might not be advisable in patients who present with life-threatening arrhythmias, nor should it be used for secondary prevention purposes. However, for patients with coronary artery disease, depressed LVEF, and NSVT, PES should be considered a valid tool for risk stratification and primary prevention, at least until the results of the MADIT II trial suggest otherwise.

Signal-Averaged Electrocardiography

The prognostic significance of late potentials has been demonstrated in several studies.[107-110] In patients with an abnormal SAECG, the incidence of sudden cardiac death, ventricular fibrillation, or sustained ventricular tachycardia has been reported to range from 17% to 29%; in patients with a normal SAECG, the incidence ranges from 0.8% to 3.5%.[107]

Signal-averaged electrocardiography has been shown to be a predictor of sudden cardiac death and sustained ventricular tachycardia in post-MI patients, independent of LV function and ventricular ectopic activity and unaffected by transient hemodynamic abnormalities.[108-110] Although the negative predictive value of a normal SAECG is good, the application of SAECG in risk stratification for sudden cardiac death is limited by its low positive predictive value in post-MI patients and by its low sensitivity in patients with nonischemic cardiomyopathies.[111-113] Therefore, SAECG is useful in identifying those post-MI patients who are at high risk for sudden cardiac death, but its role for patients with idiopathic dilated cardiomyopathy and CHF is less certain.

Antiarrhythmic Drug Therapy

The use of antiarrhythmic drugs in heart failure patients is associated with certain concerns. The 1st and usually the most troubling concern is that the

depression of ventricular function by the antiarrhythmic drugs will exacerbate the heart failure. The only drugs that appear to be free of this problem are quinidine and amiodarone.[71,114] Another concern is proarrhythmia, which is more likely in patients with impaired LV function.[115]

Class I Drugs. Physicians have been reluctant to use class I drugs in patients with underlying cardiac disease, including heart failure.[64] Their reluctance stems from the findings of the CAST* study and from the increased mortality rate among post-MI patients with VPDs who have been treated with class IC drugs. Also, investigators in the propafenone arm of the CASH* trial reported a tendency towards increased mortality rates when propafenone was administered to patients with life-threatening ventricular tachycardia or ventricular fibrillation.[116]

Class III Drugs. Next to beta blockers, class III drugs are the most widely used agents in the treatment of CHF. Amiodarone, for example, has several advantages. It has a potent antiarrhythmic effect in both the atrium and the ventricle, but it does not slow conduction and it has no adverse effect on ventricular function. Hamer and associates[117] found that amiodarone suppressed NSVT and significantly reduced mortality rates in heart failure patients who had no sustained ventricular arrhythmia. Such data and the promising results achieved with amiodarone in post-MI patients[118-120] led to large controlled studies to assess the value of amiodarone in the prevention of sudden cardiac death among CHF patients.

In the GESICA* study, 516 CHF patients (New York Heart Association [NYHA] functional class II to IV) with LVEF less than 35% who were receiving optimal standard heart failure therapy were randomly assigned to treatment with either amiodarone (300 mg/day) or the standard medical therapy that they were already on.[121] There were 87 deaths in the amiodarone-treated group, and 106 deaths in the control group (28% risk reduction; 95% confidence interval of 4% to 45%; *P*=0.02). The reduction in the number of deaths reflected improved rates of sudden death and death due to worsening heart failure.[121] However, these results were not reproducible in the CHF-STAT trial, which examined the use of amiodarone in CHF patients (NYHA functional class II to IV), LVEF less than 40%, and asymptomatic ventricular arrhythmia (more than 10 VPDs/hr). In CHF-STAT,[122] 674 patients were randomly assigned to treatment with either amiodarone (400 mg/day maintenance dose) or a placebo. There was no significant difference in the rates of overall mortality or sudden cardiac death between the 2 groups, despite

the improved LV function and suppressed ventricular arrhythmias in the amiodarone-treated group. There was a trend toward a reduced mortality rate among patients with nonischemic cardiomyopathy who received amiodarone; the different results obtained between the GESICA study and the CHF-STAT trial can, then, be attributed to the much higher percentage of patients with nonischemic cardiomyopathy in the GESICA study.[122]

Two studies have focused on the efficacy of amiodarone in the prevention of sudden cardiac death and malignant ventricular arrhythmia in high-risk post-MI patients. The EMIAT* study[123,124] monitored 1,486 patients aged 18 to 75 years who had suffered MI 5 to 21 days previously, whose LVEF was 40% or less, and who had ventricular ectopic beats on Holter monitoring. Patients were randomly assigned to treatment with either amiodarone or a placebo. The endpoints of the study were all-cause mortality, cardiac-related mortality, arrhythmic death, and arrhythmic death together with resuscitated sudden cardiac death. There was no difference in the rates of all-cause or cardiac-related mortality between the 2 groups, but the amiodarone arm experienced a reduced rate of arrhythmic death and a reduced rate of arrhythmic death together with resuscitated sudden cardiac death. The 2nd study,[125] CAMIAT*, studied 1,202 patients who had suffered MI 6 to 45 days previously and for whom electrocardiography showed at least 10 ventricular ectopic beats per hour or NSVT of more than 3 beats. A history of CHF was present in 21% to 26% of the patients. Patients were randomly assigned to treatment with either amiodarone or a placebo. The primary endpoint was arrhythmic death, with a secondary endpoint of all-cause mortality. There was no difference in all-cause mortality between the 2 groups; however, amiodarone reduced the cumulative risk of arrhythmic death or resuscitated ventricular fibrillation by 48.5% (a 32.6% reduction in arrhythmic death, 27.4% reduction in cardiac death, and 21% reduction in all-cause mortality).

The role of dofetilide, a class III antiarrhythmic agent, in the treatment of CHF patients has recently been evaluated in the DIAMOND* trial.[126] Preliminary data, however, have revealed no benefit in the dofetilide arm of the trial.

Other Drugs. The beneficial role of beta blockers in the reduction of overall and sudden cardiac death in heart failure patients has been shown in several recent trials.[127-132] In a study of carvedilol,[133] 1,052 CHF patients (NYHA functional class II to IV) were

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* CAST = Cardiac Arrhythmia Suppression Trial; CASH = Cardiac Arrest Study Hamburg; GESICA = Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina

* EMIAT = European Myocardial Infarct Amiodarone Trial; CAMIAT = Canadian Amiodarone Myocardial Infarction Arrhythmia Trial; DIAMOND = Danish Investigators of Arrhythmia and Mortality ON Dofetilide

randomly assigned to treatment with either carvedilol or a placebo. After 25 months the mortality rate was 8.2% in the placebo group, and 2.9% in the carvedilol-treated group (a 67% reduction). The reduced mortality rate in the carvedilol arm reflects both a reduced rate of death from progressive CHF and a reduced rate of sudden death. A detailed discussion of the benefits of beta blockers in the treatment of CHF is beyond the scope of this article.

Some large placebo-controlled studies have shown a reduction in sudden death among patients treated with angiotensin-converting enzyme (ACE) inhibitors.[134,135] Furthermore, Fletcher and associates[136] reported that the ACE inhibitor enalapril decreased the occurrence of baseline ventricular tachycardia at 3 months and the emergence of new ventricular tachycardia at 1 and 2 years. These data raise the possibility that ACE inhibitors may have a direct antiarrhythmic effect in CHF patients. However, this hypothesis has been difficult to prove and has not been supported by the much larger SOLVD* trial.[137,138]

Summary. While the available data discourage the use of class I antiarrhythmic agents to treat patients with LV dysfunction, some studies have shown amiodarone, a class III antiarrhythmic agent, to be beneficial in the reduction of arrhythmic and overall cardiac-related mortality rates, especially in patients with dilated cardiomyopathy; however, the data regarding amiodarone are not consistent. Based on current data, amiodarone is not recommended for routine use in post-MI patients, or for those who have depressed LVEF or complex ventricular arrhythmia. The beneficial role of beta blockers, especially carvedilol, in the reduction of life-threatening arrhythmia and sudden cardiac death is widely accepted and is supported by current data.

Device Therapy

The efficacy of defibrillators in the termination of ventricular arrhythmias is well established.[139-143] Also, defibrillator therapy effectively reduces the annual incidence of sudden cardiac death among patients with severe underlying cardiac disease,[140,141] and among patients without significant structural heart disease.[142]

Despite the ability of defibrillator therapy to effectively reduce the rate of sudden cardiac death, its use to enhance long-term survival in patients with depressed LV function is controversial. Patients with LV dysfunction have a high risk of tachyarrhythmic death, and other causes of death such as pump failure and stroke are also very common. The effect of these factors on overall survival despite the use of ICD therapy is often questioned.

*SOLVD = Studies of Left Ventricular Dysfunction

Primary Prevention Trials

Several recent or ongoing primary prevention trials have focused on the role of prophylactic ICD implantation and the high risk of sudden death in patients with LV dysfunction (Table IV).

MADIT. As discussed earlier, the presence of NSVT in patients with depressed LV function, coronary artery disease, and inducible nonsuppressible ventricular tachycardia in electrophysiology study is a predictor of a poor prognosis (2-year mortality rate of 30%).[143] MADIT was designed to determine the benefits, if any, of prophylactic ICD implantation in these patients. Over a period of 5 years, 196 patients from 32 centers in the United States and Europe were enrolled in the MADIT trial. Requirements included prior MI (at least 3 weeks previously), ejection fraction of 35% or less, NYHA functional class I to III, a documented episode of NSVT, and inducible nonsuppressible sustained ventricular tachycardia. The average ejection fraction among MADIT patients was 26%, and half of the patients had evidence of CHF. The patients were randomly assigned to treatment with either ICD implantation (n=95) or conventional medical therapy (n=101). MADIT was terminated early by the safety monitoring committee because of significantly improved survival in the ICD arm.[143] There were 15 (15.8%) deaths in the ICD group and 39 (38.6%) deaths in the conventional group (hazard ratio 0.46; 95% confidence interval 0.26 to 0.82; P=0.009). The investigators concluded that in the selected population with LV dysfunction and coronary artery disease, ICD therapy was superior and increased survival.

Four major criticisms have been raised about the MADIT trial. First, only approximately 2% to 3% of MI survivors satisfy the inclusion criteria of MADIT; therefore, this study might be clinically applicable to only a small group of patients. Second, approximately 30% of the patients who initially received amiodarone therapy discontinued it, and 25% of patients assigned to the ICD group were taking amiodarone by the end of the study. These modifications make it more difficult to compare the 2 arms. The 3rd criticism is that beta blockers, known to prolong survival in post-MI patients, were administered to more patients in the ICD arm than in the conventional therapy arm. The MADIT investigators believe that the reduction in overall mortality rates in their study cannot be attributed to the use of beta blockers in the ICD arm, and cite the BHAT trial,[147] which reported a difference of 2.5% in mortality rates between the placebo arm and the propranolol arm over a 27-month period. Finally, applying the complicated inclusion criteria of the MADIT trial (i.e., inducibility by PES and evaluation of suppressibility of induced ventricular tachycardia) is impractical in daily clinical settings.

TABLE IV. Prospective Multicenter Intracardiac Defibrillator Primary Prevention Trials

Study	Patient Inclusion Criteria	Endpoint(s)	Treatment Arms	Key Results
MADIT[143]	•Q-wave MI ≥3 weeks •Asymptomatic NSVT •LVEF ≤0.35 •Inducible, nonsuppressible VT on EPS w/procainamide •NYHA class I-III	•Overall mortality •Costs and cost-effectiveness	•ICD (n=95) •Conventional therapy (n=101)	•ICDs reduced overall mortality by 54% •ICDs cost $16,900 per life-year saved versus conventional therapy
CABG Patch[144]	•Scheduled for elective CABG surgery •LVEF <0.36 •Abnormal SAECG	•Overall mortality	•ICD (n=446) •Standard treatment (n=454)	•Survival was not improved by prophylactic implantation of ICD at time of elective CABG
MUSTT[145]	•CAD •EF ≤0.40 •NSVT •Inducible VT or VF	•Sudden arrhythmic death or spontaneous sustained VT	•ICD in nonsuppressible group •Antiarrhythmic drug therapy in suppressible group •No therapy	•Ongoing
SCD HeFT	•Ischemic or nonischemic dilated cardiomyopathy •NYHA class II-III •EF ≤0.35	•Total mortality •Arrhythmic mortality •Costs •Quality of life	•ICD •Amiodarone •Placebo	•Ongoing
Cardio-Myopathy Study[146]	•Dilated nonischemic cardiomyopathy •LVEF ≤0.3 •NYHA class II-III	•Total mortality •Sudden death •Serious arrhythmia	•ICD •Standard treatment	•Ongoing
DEFIBRILLAT	•CHF patients awaiting heart transplantation	•Total mortality •Serious arrhythmias	•ICD •Standard treatment	•Ongoing

CABG = coronary artery bypass grafting; CAD = coronary artery disease; CHF = congestive heart failure; DEFIBRILLAT = Defibrillators as a Bridge to Transplantation; EF = ejection fraction; EPS = electrophysiology study; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MADIT = Multicenter Automatic Defibrillator Implantation Trial; MI = myocardial infarction; MUSTT = Multicenter Unsustained Tachycardia Trial; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; SAECG = signal-averaged electrocardiogram; SCD HeFT = Sudden Cardiac Death in Heart Failure Trial; VF = ventricular fibrillation; VT = ventricular tachycardia

Despite these concerns, the MADIT trial has major implications: it suggests that prophylactic ICD therapy cannot only save lives in a selected group of patients with LV dysfunction, but it might save more lives than can be saved with amiodarone therapy.

MADIT II. The MADIT II trial has been designed to expand and simplify the narrow, complicated inclusion criteria of the MADIT trial by eliminating risk stratification by PES. The MADIT II trial is currently enrolling patients. In this trial, post-MI patients with ejection fractions less than 30% and complex VPDs will be randomly assigned to receive either ICD therapy or conventional therapy.

CABG Patch. In the CABG Patch* trial,[144] the prophylactic role of ICDs was evaluated in a population of high-risk patients with established coronary artery disease, depressed LV function, and abnormalities on SAECG. The trial was based on evidence that patients with depressed LVEF have a 20% to 30% incidence of sudden cardiac death, and that coronary revascularization does not appear to improve this

*CABG Patch = Coronary Artery Bypass Graft Patch

statistic. In other words, surgical revascularization improves ischemia-related ventricular tachycardia, but has minimal effect on scar-related ventricular tachycardia in patients with coronary artery disease. Nine hundred patients younger than 80 years of age with LVEF of less than 36% and filtered QRS duration of more than 114 ms on SAECG were randomly assigned either to therapy with prophylactic implantation of an ICD during elective coronary artery bypass surgery (n=446) or to the control group (n=454). The primary endpoint was overall mortality. Over an average follow-up period of 32 ± 16 months, there were 101 deaths in the ICD group (71 from cardiac causes), and 95 deaths in the control group (72 from cardiac causes). The hazard ratio for overall mortality was 1.07 (95% confidence interval, 0.81 to 1.42; P=0.64). CABG Patch investigators concluded that in this patient population, survival was not improved by prophylactic ICD implantation during elective coronary artery bypass surgery.

Comparison of MADIT and CABG Patch. While there was no significant difference in basic patient characteristics (i.e., age, sex, ejection fraction, history of CHF, and extent of coronary artery disease) between the MADIT and CABG Patch trials, NSVT was present in only 30% of CABG Patch patients (based on an average of 16 hours of Holter monitoring), but was present in 100% of MADIT patients (real difference of 65% vs. 100%). Signal-averaged electrocardiography was abnormal in 100% of the CABG Patch patients, as compared to 60% of the MADIT patients. All of the patients in the CABG Patch trial had been revascularized, compared to only two-thirds of the MADIT patients. Also, the rate of inducibility by PES in the CABG Patch trial was lower than the 100% rate in the MADIT trial. Only 90 patients in the CABG Patch trial had PES during enrollment, but the inducibility rate is estimated, using mathematical models, to be about 22%. Considering these facts, the different results of the MADIT and CABG Patch trials can be explained in 2 ways. First, compared to PES, SAECG might not be a good risk stratification strategy for subsequent arrhythmic and overall mortality in this subset of patients. If we accept that patients with abnormal SAECG have a low inducibility rate, and consider that patients with low ejection fraction and inducible ventricular tachycardia are 4 times more likely to experience arrhythmic events, then the difference between the results of these 2 studies can be attributed to the lower percentage of patients with inducible ventricular tachycardia in the CABG Patch trial. Second, revascularization can reduce the number of arrhythmic deaths by preventing the ischemic triggering that causes arrhythmogenic scars to express themselves. And revascularization itself might have a beneficial effect on overall mortality rates with other unknown mechanisms. The

fact that the 2-year mortality rate in the control arm of the CABG Patch trial was lower than in the control arm of the MADIT trial further supports these hypotheses.

CABG Patch II. The CABG Patch II trial has been designed to evaluate these hypotheses. In CABG Patch II, all survivors of the CABG Patch trial will undergo electrophysiology study. If the inducibility rate of survivors is far beyond the mathematical estimation of 22%, it will further support the 2nd hypothesis. This study is currently enrolling patients.

MUSTT. The MUSTT Trial[145] is not a direct study of the efficacy of the ICD, but the inclusion of device therapy in one arm of the trial offers an opportunity to examine the usefulness of ICD implantation. The primary hypothesis is that electrophysiology-guided therapy can reduce the incidence of sudden arrhythmic death or spontaneous episodes of sustained ventricular tachycardia. Additionally, MUSTT investigators hope 1) to quantify the risk of sudden cardiac death in untreated patients with LVEF of less than 40%, NSVT, and inducible sustained ventricular tachycardia, and 2) to confirm the low risk of sudden cardiac death in patients without inducible sustained ventricular tachycardia. Also, the role of SAECG in comparison to PES will be evaluated. Patients with coronary artery disease, LVEF of 40% or less, and NSVT (with or without a positive SAECG) receive PES. Those who are inducible are randomly assigned to receive either electrophysiology-guided therapy or no antiarrhythmic therapy. The electrophysiology-guided group is further subdivided into 2 groups: patients who respond to drugs, and those who do not. The patients who respond to drugs are monitored while receiving the appropriate drug, while the patients who do not respond to drugs undergo ICD implantation. Enrollment of approximately 700 patients for MUSTT began in 1992 and was completed in 1996. The results of this trial are pending and, with a minimum follow-up period of 2 years, this study is expected to substantially increase our understanding of the roles of PES and SAECG in risk stratification, and the role of electrophysiology-guided therapy in the subset of patients with depressed LV function, coronary artery disease, and nonsustained ventricular arrhythmia.

SCD-HeFT. The SCD-HeFT* trial is another ongoing prospective primary prevention trial in patients with LV dysfunction. This trial focuses on the benefits of prophylactic amiodarone or implantable defibrillator therapy versus a placebo, when each technique is combined with maximized heart failure therapy. The hypothesis in this trial sponsored by the National Institutes of Health is that in the popula-

*SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial

tion with moderate heart failure as many as 50% of the sudden deaths might be preventable with prophylactic amiodarone or defibrillator therapy, or both.

Twenty-five hundred patients older than 18 years of age with symptomatic NYHA functional class II or III heart failure (ischemic or nonischemic) of at least 3 months' duration and LVEF of 35% or less are treated maximally with ACE inhibitors or vasodilators, or both, and randomly allocated in equal proportions to 3 different treatment arms over 2.5 years. The 1st arm of the study is the control arm, which consists of conventional heart failure therapy and a placebo. The 2nd arm combines conventional therapy with amiodarone. In these 2 arms of the study amiodarone and placebo are delivered in a double-blind fashion. The 3rd arm of the study combines conventional therapy and implantation of a single-lead pectoral ICD. Implantation of the ICD is usually performed on an outpatient basis. Patients with NYHA functional class I and IV heart failure, a life expectancy of less than 1 year, or restrictive, hypertrophic, or infiltrative cardiomyopathy are excluded. The primary endpoint of the study is all-cause mortality based on a 2.5-year follow-up. Morbidity (mortality and hospitalizations), economics, and quality of life will be evaluated separately as secondary endpoints. Treatment arms will be compared using an intention-to-treat analysis.

Enrollment for this trial began in 1996 and by May of 1998 as many as 208 patients were enrolled. It is estimated that enrollment will be completed by the year 2000 and, allowing time for a 5-year follow-up period, preliminary results might be available as early as the year 2002. This study is expected to shed more light on the mechanisms of cardiac-related and arrhythmic mortality, the significance of primary bradyarrhythmias, and the mechanisms surrounding the onset of ventricular tachycardia and ventricular fibrillation in patients with cardiomyopathy (by using the memory logs).

CardioMyopathy Study. The ongoing CardioMyopathy Study[146] is based on evidence that patients with dilated cardiomyopathy have a high incidence of sudden cardiac death, and that there are few predictors of serious arrhythmia apart from the degree of LV impairment. Prophylactic ICD implantation might have the potential to extend the life of these patients or to serve as a bridge to transplantation. The study includes patients between 18 and 70 years of age with dilated cardiomyopathy, an LVEF of 30% or less, and symptomatic heart failure (NYHA functional class II or III). Patients should not have had symptomatic ventricular arrhythmias before their entry into the study. Patients are excluded if their diagnosis is more than 9 months old, if they have significant coronary artery disease, or if they expect

to undergo heart transplantation within 6 months. Patients with class I or IV heart failure are also excluded. The patients are randomly divided into 2 groups: one group of patients receives ICDs, and the other group does not. Patients are then monitored for the primary endpoints of the study: mortality, sudden death, and serious arrhythmia. This study was started in 1991 and is ongoing.

DEFIBRILLAT. The DEFIBRILLAT* study is currently in the planning stages. It will enroll CHF patients who are awaiting cardiac transplantation, and will randomly assign them to treatment with or without ICD implantation. The primary endpoints of this study are mortality and serious cardiac arrhythmia.

Secondary Prevention Trials

The 3 major secondary prevention trials are AVID*, CASH, and CIDS* (Table V). A substantial number of patients enrolled in these trials had significant LV dysfunction, although the target population was not limited to patients with LV dysfunction (Table VI). None of these trials had the power to enable the study of subsets of patients with normal and abnormal ejection fractions. However, a meta-analysis of these 3 trials is planned to assess the role of ICD implantation in patients with LV dysfunction. Preliminary data from an AVID subanalysis suggest that ICDs might have a more beneficial effect in patients with lower ejection fractions.

AVID. In the AVID study,[148] mean LVEF was 32% ± 13%, and almost 55% of patients had clinical CHF (48% in NYHA functional class I or II, and 7% in NYHA functional class III). The study enrolled 1,016 patients who had either been resuscitated from near-fatal ventricular fibrillation (45%) or undergone cardioversion from sustained ventricular tachycardia (55%). Patients who had ventricular tachycardia also had either syncope or other serious cardiac symptoms, and LVEF of 40% or less. The patients were randomly assigned to treatment with either class III antiarrhythmic drugs (primarily empirically determined doses of amiodarone) or ICD implantation. The primary endpoint was overall mortality. The study was terminated prematurely by the Data and Safety Monitoring Board when analysis revealed that the difference in the primary outcome variable between the 2 groups had crossed the statistical boundary.

The ICD group experienced greater overall survival when compared with the group that received medical therapy. Unadjusted estimated survival rates for the ICD and medical therapy groups, respectively, were 89.3% and 82.3% at 1 year, 81.6% and 74.7%

* DEFIBRILLAT = Defibrillators as a Bridge to Transplantation;
AVID = Antiarrhythmics Versus Implantable Defibrillators;
CIDS = Canadian Implantable Defibrillator Study

TABLE V. Prospective Multicenter Intracardiac Defibrillator Secondary Prevention Trials

Study	Patient Inclusion Criteria	Endpoint(s)	Treatment Arms	Key Results
AVID[148]	•VF; or •Sustained VT w/syncope; or •Sustained VT w/o syncope; and LVEF ≤0.4; and SBP <80 mmHg, chest pain, or near syncope	•Overall mortality •Quality of life •Cost and cost-effectiveness	•ICD therapy (n = 29) •EP or Holter guided sotalol or empiric amiodarone	•ICDs reduced total mortality 39% after 1 year, 27% after 2 years and 31% after 3 years compared with antiarrhythmic drugs
CASH[116]	•Survivors of sudden cardiac death documented to be associated with VF; or •Hemodynamically significant sustained VT	•Total mortality •Recurrence of sudden cardiac death •Arrhythmic mortality	•ICD •Propafenone •Metoprolol •Amiodarone	•Propafenone arm was associated with excess mortality and was discontinued •No significant mortality difference between amiodarone and metoprolol •ICD decreased total mortality by 63% in 1 year and 37% in 2 years compared to combination arms of amiodarone and metoprolol
CIDS[149]	•Survivors of sudden cardiac death documented to be associated with VF; or •VT with syncope; or •Sustained VT and LVEF <0.35 •Syncope of unknown cause and inducible VT in EPS and LVEF <0.35	•All-cause mortality •Arrhythmic death	•ICD •Amiodarone	•ICD decreased all-cause mortality slightly but not significantly •Results were consistent with AVID and CASH

AVID = Antiarrhythmics Versus Implantable Defibrillators; CASH = Cardiac Arrest Study Hamburg; CIDS = Canadian Implantable Defibrillator Study; EP = electrophysiology; EPS = electrophysiology study; ICD = implantable cardioverter-defibrillator; LVEF = left-ventricular ejection fraction; SBP = systolic blood pressure; VF = ventricular fibrillation; VT = ventricular tachycardia

TABLE VI. Mean Left-Ventricular Ejection Fraction in Secondary Prevention Trials

Study	LVEF	
	ICD Arm	Amiodarone Arm
AVID	32%	31%
CASH	48%	44%
CIDS	33%	33%

AVID = Antiarrhythmics Versus Implantable Defibrillators; CASH = Cardiac Arrest Study Hamburg; CIDS = Canadian Implantable Defibrillator Study; ICD = implantable cardioverter-defibrillator; LVEF = left-ventricular ejection fraction

at 2 years, and 75.4% and 64.1% at 3 years (P <0.02). The corresponding reductions in mortality (95% confidence limits) in the ICD group were 39% ± 20% at 1 year, 27% ± 21% at 2 years, and 31% ± 21% at 3 years. A preliminary analysis of subsets of patients also suggests that the beneficial effect of ICD implan-

tation on total survival might be much greater in patients with lower LVEF.

The results of this trial seem to indicate that ICD implantation is a reasonable therapy for patients with LV dysfunction who present with aborted sudden cardiac death or hemodynamically unstable ventricular tachycardia. However, the role of ICD implantation for patients in the advanced stages of congestive heart failure (NYHA class IV) is unclear. These patients have not been included in the secondary prevention trials. Their limited life expectancy makes it very difficult, statistically, to confirm the beneficial role of ICD implantation in preventing arrhythmic deaths. Also, it is widely believed that primary bradyarrhythmias and electromechanical dissociation play a much more important role than tachyarrhythmias in the arrhythmic deaths of these patients; tachyarrhythmias are believed to be manifestations of the failing heart. Therefore, it seems unreasonable to consider defibrillator therapy for these patients, other than as a bridge to transplantation.

CASH. The CASH study[116] was initiated in 1987 and was originally designed to compare ICD therapy

with medical therapy using propafenone, amiodarone, and metoprolol. This study included survivors of sudden cardiac death caused by documented ventricular fibrillation, and patients who presented with hemodynamically significant ventricular tachycardia. The main exclusion criterion was myocardial infarction within 72 hours of sudden cardiac death. The mean ejection fraction was 46%, and approximately 75% of the patients had coronary artery disease. The endpoints of the study were total mortality based on intention to treat, recurrence of sudden cardiac death, and sudden cardiac death mortality.

In July of 1992, an interim analysis indicated an excessive mortality rate in the propafenone arm when compared with the ICD arm, and the propafenone arm was dropped. The amiodarone, metoprolol, and ICD arms of the trial continued, and follow-up evaluations were conducted for a minimum of 2 years after randomization for 349 patients. Preliminary data were recently presented, and they revealed that ICD implantation significantly decreased overall mortality by 63% in the 1st year of follow-up. The 2-year mortality rate in the ICD group was 12.1%, versus 19.6% in the combined drug therapy groups (37% reduction in 2-year overall mortality, P=0.047). There was no significant difference in mortality rate between the amiodarone and metoprolol groups. The average ejection fraction in this study was 10% higher than in AVID because this study focused mainly on patients who presented with ventricular fibrillation. The results of this trial were consistent with the results of the AVID and CIDS trials.

CIDS. In CIDS,[149] 659 patients were randomly assigned to receive either ICD therapy (n=328) or amiodarone (n=331). As with the AVID trial, this study was not restricted to patients with CHF. However, a significant number of patients with LV dysfunction were enrolled (mean ejection fraction: 33%). The study population included cardiac arrest survivors (55%), patients with sustained ventricular tachycardia and ejection fraction less than 35% (25%), patients with syncope associated with ventricular tachycardia (10%), and patients who had syncope that was not documented to be associated with ventricular tachycardia but who had inducible ventricular tachycardia at electrophysiologic study (10%). The study endpoint was all-cause mortality, with a 2nd endpoint of arrhythmic death. By the end of 5 years after enrollment, 22% of patients in the amiodarone group had received a crossover ICD, and 30% of the ICD patients had received crossover amiodarone. All-cause mortality was slightly, but not significantly, lower in the ICD group (approximately 27% at 4 years with ICD, versus approximately 33% with amiodarone; P=0.07). Despite a modest but not statistically significant reduction in mortality rate with ICD therapy, the main significance of this trial

is that its results are consistent with data from the AVID and CASH trials. Also, subanalysis has revealed that patients who presented with syncope and had inducible ventricular tachycardia in electrophysiology study had the same survival curves as the subset of patients who presented with ventricular fibrillation. Evaluations of cost effectiveness issues and the effects of these therapies on the quality of life have not been completed.

Summary

The benefit of defibrillator therapy has been well established for patients with LV dysfunction (ejection fraction less than 35%), coronary artery disease, NSVT, and inducible and nonsuppressible ventricular tachycardia. Implantable cardioverter-defibrillator therapy is also indicated for all CHF patients in NYHA functional classes I, II, and III who present with aborted sudden cardiac death, or ventricular fibrillation, or hemodynamically unstable ventricular tachycardia—and also in patients with syncope with no documented ventricular tachycardia but with inducible ventricular tachycardia at electrophysiology study. The ongoing MADIT II trial was designed to evaluate the benefit of prophylactic ICD implantation in these patients (ejection fraction less than 30%, coronary artery disease, and NSVT) without prior risk stratification by PES.

The CABG Patch trial concluded that prophylactic placement of an ICD during coronary artery bypass grafting in patients with low ejection fraction and abnormal SAECG is not justifiable. Except for the indications described above, ICD implantation has not been proved to be beneficial as primary or secondary therapy. Until more data are available, patients should be encouraged to enroll in the ongoing clinical trials.

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